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METHOD OF PREPARATION OF OPTICALLY ACTIVE ALCOHOLS

[FIELD OF THE INVENTION]

The present invention relates to a method of preparing a chiral alcohol with optical activity, and more particularly, to a method of preparing a chiral alcohol with optical activity and high optical purity by using metal catalyst and enzyme catalyst in one reaction vessel.

[BACKGROUND OF THE INVENTION]

A method for steroselective synthesis of one enantiomer is an important tool in synthetic chemistry. Especially, since optically active alcohols are important in asymmetric synthesis, the presentation of stereoselective synthesis of an optically pure alcohol is very important.

Conventional stereoselective syntheses of optically active alcohol include a method of synthesizing the alcohol using chiral metal catalyst or ligand and a method of performing optical resolution using enzyme. However, the chiral metal catalyst or ligand is very costly and the method of kinetic resolution has a low yield of less than 50%.

In order to overcome the above shortcomings, a dynamic kinetic resolution (DKR) by the combination of enzyme catalyst and metal catalyst has been suggested (Persson, B. A.; Larsson, A. L. E.; Ray, M. L.; Baeckvall, J.-E. *J. Am. Chem. Soc.* 1999, 121, 1645.; Lee, D. H.; Huh, E. A.; Kim, M.–J.; Jung, H. M.; Koh, J. H.; Park, J. *Org. Lett.* 2000, 2, 2377.; Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.–J.; Park, J. *Angew. Chem. Int. Ed.* 2002, 41, 2373.).

The above method uses both enzyme catalyst and metal catalyst and thus does not need chiral ligand. The method is effective asymmetric synthesis in that it can overcome the limitations of the previous simple kinetic resolution method. However, since it uses lipase as enzyme catalyst, only ®-enantiomer can be synthesized. That is to say, in the case of 1-phenylethanol, only an ®-chiral alcohol can be synthesized and an (S)-chiral alcohol is not obtained.

However, (S)-chiral alcohol which is counter enantiomer synthesized using lipase is also an important optical enantiomer in asymmetric synthesis in the field of fine chemistry where pharmaceutical drugs, pesticides, cosmetics, food additives and so on are synthesized. Therefore, a selective synthesis method of such an

(S)-enantiomer has been seriously needed. However, up to now a synthesis method of (S)-chiral alcohols with high optical purity and high yield has not been suggested.

[DETAILED DESCRIPTION OF THE INVENTION]

The present invention provides a method of synthesizing (S)-chiral alcohol enantioselectively with a high optical purity and a high yield. The (S)-chiral alcohol is an counter enantiomer of a chiral alcohol which can be obtained using lipase in the conventional dynamic kinetic resolution method.

In order to attain the above aspect and other aspects, the present invention provides a method of preparing (S)-chiral alcohol. The method includes:

(a) reacting in organic solvent a compound of a following chemical formula 1 as a starting material,

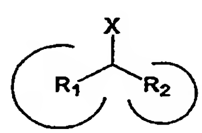
a racemization metal catalyst,

an acyl donor being capable of acylating an alcohol compound, and

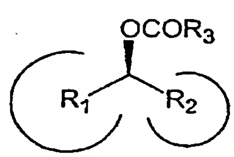
a protein hydrolysis enzyme being capable of stimulating the enantioselective acylation of a racemic compound to obtain a chiral ester compound of chemical formula 3; and

(b) hydrolyzing the chiral ester compound of chemical formula 3 to obtain (S)-chiral alcohol.

[chemical formula 1]



[chemical formula 3]



where X is –OH or =O,

R_1, R_2 and R_3 are independently substituted or unsubstituted C_1-C_{15} alkyls, substituted or unsubstituted C_2-C_{15} alkenyls, substituted or unsubstituted C_2-C_{15}

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alkynyls, substituted or unsubstituted C_5-C_{18} aryls, substituted or unsubstituted C_6-C_{18} arylalkyls, substituted or unsubstituted C_2-C_{20} heterocycles, substituted or unsubstituted C_3-C_{20} heteroarylalkyls, substituted or unsubstituted C_3-C_{15} cycloalkyls, substituted or unsubstituted C_3-C_{15} cycloalkenyls, substituted or unsubstituted C_6-C_{15} cycloalkynyls, or substituted or unsubstituted C_3-C_{20} heterocycloalkyls, and R_1 and R_2 can be linked together. R_1 and R_2 may be linked together to form, specifically, a substituted or unsubstituted C_7-C_{20} fused ring or a substituted or unsubstituted C_5-C_{20} hetero fused ring.

In the above formulas, a size of a circular arc may indicate that R_1 group is larger than R_2 group.

In the preparation method, when a starting material is a compound having a chemical formula 1 such as a ketone where X is =O, a hydrogen donor may be added in the (a) step.

The preparation is described in two cases: when the compound of chemical formula 1 is the compound of the chemical formula 1a having an alcohol group and when the compound of chemical formula 1 is the compound of the chemical formula 1b having a ketone group.

In a case where the compound of chemical formula 1 is the compound of the chemical formula 1a, the method includes:

(a) reacting in organic solvent the compound of the following chemical formula 1a;

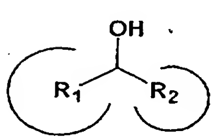
a racemization metal catalyst,

an acyl donor being capable of acylating an alcohol compound, and

a protein hydrolysis enzyme being capable of stimulating the enantioselective acylation of a racemic compound to obtain a chiral ester compound of chemical formula 3; and

(b) hydrolyzing the chiral ester compound of chemical formula 3 to obtain an (S)-chiral alcohol.

[chemical formula 1a]



where, R_1 and R_2 are the same as defined in chemical formula 1.

In the case where a compound of chemical formula 1 is the compound of the chemical formula 1b, the method includes:

(a) reacting in organic solvent the compound of the following chemical formula 1b, a racemization metal catalyst,

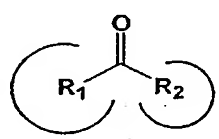
a hydrogen donor being capable of reducing a ketone to an alcohol,

an acyl donor being capable of acylating an alcohol compound, and

a protein hydrolysis enzyme being capable of stimulating the enantioselective acylation of a racemic compound to obtain a chiral ester compound of chemical formula 3; and

(b) hydrolyzing the chiral ester compound of chemical formula 3 to obtain an (S)-chiral alcohol.

[chemical formula 1b]



R_1 and R_2 may defined as defined above in chemical formula 1.

The preparation method of the present invention has representative features as follows: an (S)-chiral alcohol which is impossible to prepare using lipase in conventional dynamic kinetic resolution method can be obtained by using a protein hydrolysis enzyme instead of the lipase in (a) step. Step (a) may be a one-pot reaction which is performed in one reaction vessel.

In step (a), the compound of chemical formula 1 is used as a substrate in an organic solvent, and dynamic kinetic resolution is performed by the combination of metal catalyst and enzyme catalyst, protein hydrolysis enzyme, in one reaction vessel to obtain an (S)-chiral ester having optical activity. The reaction described in step (a) is a one-pot reaction where all the reaction materials react simultaneously without separation of reaction intermediates. When the substrate is a compound of chemical formula 1b having a ketone group, a hydrogen donor is added, and thus the ketone group is reduced to an alcohol group before the above described reaction. This reaction is also one-pot reaction where all reactions after t

reduction are performed simultaneously.

An (S)-chiral ester prepared in step (a) is converted to an (S)-chiral alcohol by conventional hydrolysis.

The preparation of a chiral compound of chemical formula 3 is described in more detail.

The following compounds are mixed in a solvent to prepare a chiral compound having chemical formula 3: a substrate including a compound having chemical formula 1 with either an alcohol or a ketone group; metal catalyst which stimulates a reduction reaction of the ketone to an alcohol when the compound of chemical formula 1 has a ketone group, and stimulates racemization reaction of an alcohol; hydrogen donor for reducing ketone group when the compound of chemical formula 1 has ketone group; acyl donor being capable of acylating an alcohol compound of chemical formula 1; and protein hydrolysis enzyme being capable of leading the enantioselective acylation of one enantiomer of racemic alcohols.

The resulting mixture is purged with inert gas to romove oxygen, and is agitated at 0°C to 100°C, preferably at room temperature to 80°C to finish the reaction. Subsequently, the reaction mixture is worked up, and purified to obtain chiral compound of chemical formula 3.

In the above reaction, the acyl donor is a compound of the following chemical formula 2. However, acyl donor of chemical formula 2 need not be added additionally, when the compound of chemical formula 1 includes an acyl donor.

[chemical formula 2]

$$R_4O-\overset{\overset{\displaystyle O}{\|}}{C}-R_3$$

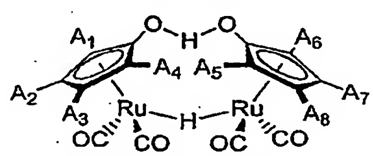
where R_3 and R_4 are independently substituted or unsubstituted C_1-C_{15} alkyls, substituted or unsubstituted C_2-C_{15} alkenyls, substituted or unsubstituted C_2-C_{15} alkynyls, substituted or unsubstituted C_5-C_{18} aryls, substituted or unsubstituted C_6-C_{18} arylalkyls, substituted or unsubstituted C_2-C_{20} heterocycles, substituted or unsubstituted C_3-C_{20} heteroarylalkyls, substituted or unsubstituted C_3-C_{15} cycloalkyls, substituted or unsubstituted C_3-C_{15} cycloalkenyls, substituted or unsubstituted C_6-C_{15} cycloalkynyls, or substituted or unsubstituted C_3-C_{20} heterocycloalkyls.

When a compound of chemical formula 1 includes an acyl donor, R_1 or R_2 may include a substituent having an -OCO-R_3 terminal group. Some compounds

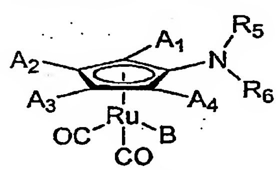
having a structure as described by chemical formula 1, for example 3-(1-hydroxyethyl)phenyl butyrate, do not need a separate addition of an acyl donor.

As described above, the metal catalyst stimulates the reduction of a compound having a structure described by chemical formula 1 and the conversion into a racemic compound. The metal catalyst includes a ruthenium complex compound, preferably ruthenium complex compound as depicted in chemical formulas 4-8 below.

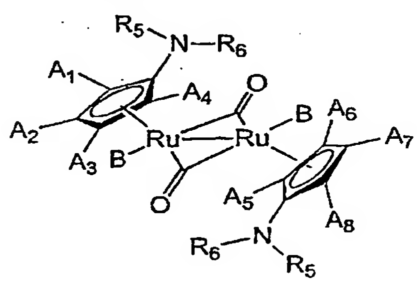
[chemical formula 4]



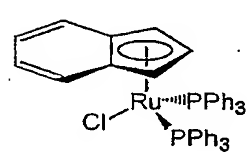
[chemical formula 5]



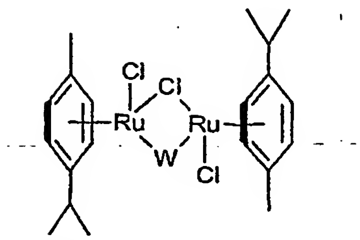
[chemical formula 6]



[chemical formula 7]



[chemical formula 8]



where, A_1, A_2, A_3, A_4, A_5, A_6, A_7 and A_8 may be hydrogen, substituted or unsubstituted C_1-C_{10} alkyls, substituted or unsubstituted C_5-C_{18} aryls, or substituted or unsubstituted C_2-C_{20} heterocycles.

R_5 and R_6 may be hydrogen, substituted or unsubstituted C_1-C_{15} alkyls, substituted or unsubstituted C_2-C_{15} alkenyls, substituted or unsubstituted C_2-C_{15} alkynyls, substituted or unsubstituted C_5-C_{18} aryls, substituted or unsubstituted C_6-C_{18} arylalkyls, substituted or unsubstituted C_2-C_{20} heterocycles, substituted or unsubstituted C_3-C_{20} heteroarylalkyls, substituted or unsubstituted C_3-C_{15} cycloalkyls, substituted or unsubstituted C_3-C_{15} cycloalkenyls, substituted or unsubstituted C_6-C_{15} cycloalkynyls, or substituted or unsubstituted C_3-C_{20} heterocycloalkyls.

B is a substituent selected from the group consisting of hydrogen, carbonyl, halogen and trifluoromethanesulfonate (herein referred to as -OTf). In some embodiments, there may be no substituent at the B site.

W is a hydrogen or a halogen.

In the above chemical formulas, examples of unsubstituted C_1-C_{15} alkyl may include methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, pentyl, iso-amyl, hexyl and so on. At least one of the alkyls can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or salt thereof, sulfonic acid or salt thereof, phosphoric acid or salt thereof, or a C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The unsubstituted C_2-C_{15} alkenyl or alkynyl may include a carbon double or a triple bond at an intermediate site or a terminal site of the alkyl as defined above. Specific examples include vinyl, propenyl, butenyl, hexenyl, ethynyl and so on. At least one hydrogen on the alkenyl or the alkynyl can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or a salt thereof, sulfonic acid or a salt thereof, phosphoric acid or a salt

thereof, or a C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The heteroalkyl may include nitrogen, sulfur, oxygen or phosphorus. Specific examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, t-butoxy, benzyloxy, naphthyloxy and triphenylmethoxy. Examples having substituents include a haloalkoxy radical such as fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. At least one hydrogen of a heteroalkyl can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or salt thereof, sulfonic acid or salt thereof, phosphoric acid or salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The aryl may include a C_5-C_{18} carbocyclic aromatic group may form a single ring or a combination of rings. The ring can be attached as a pendent group or can be fused. The term of aryl may include an aromatic radical such as phenyl, naphthyl, tetrahydronaphthyl, indane, cyclopentadienyl and biphenyl. The aryl can have at least one substituent such as hydroxyl, halo, haloalkyl, nitro, cyano, alkyl, alkoxy and low alkylamino. At least one hydrogen of aryl can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or a salt thereof, sulfonic acid or a salt thereof, phosphoric acid or a salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The arylalkyl may be defined as a compound where at least one hydrogen is substituted for using a low alkyl radical, for example methyl, ethyl, propyl and so on. Specific examples may include benzyl, phenylethyl and so on. At least one hydrogen of an arylalkyl can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or salt thereof, sulfonic acid or salt thereof, phosphoric acid or salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The heterocycle may include 4 to 20 atoms of a cyclic radical including 1, 2

or 3 heteroatoms selected from a group consisting of N, O, P and S. In some embodiments, the remaining atoms may be carbon. The term also refers to a cyclic aromatic radical where heteroatoms in a ring formation are oxidized or become quaternary to form for example N-oxide or a quaternary salt. Specific examples may include, but are not limited to thienyl, puryl, benzothienyl, pyridyl, prazinyl, pyrimidinyl, pyridazinyl, quinolinyl, quinoxalinyl, imidazolyl, puranyl, benzopuranyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyridonyl, N-alkyl-2-pyridonyl, pyrazinonyl, pyridazinonyl, pyrimidinonyl, oxazolonyl and N-oxide thereof (for example, pyridyl N-oxide, quinolinyl N-oxide), quaternary salt thereof. At least one hydrogen of the heteroatoms can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or salt thereof, sulfonic acid or salt thereof, phosphoric acid or salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The heteroarylalkyl is one where hydrogens may be substituted for using alkyl. At least one hydrogen of the heteroarylalkyl can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or a salt thereof, sulfonic acid or a salt thereof, phosphoric acid or a salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The cycloalkyl and cycloalkenyl may be a C_3-C_{15} cyclic radical. At least one hydrogen of the cycloalkyl and cycloalkenyl can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or salt thereof, sulfonic acid or salt thereof, phosphoric acid or salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The cycloalkynyl is a C_6-C_{15} cyclic radical. At least one hydrogen of the cycloalkynyl can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or a salt thereof, sulfonic acid or a salt thereof, phosphoric acid or a salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl,

cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The heterocycloalkyl may include 4 to 20 atoms of a cyclic radical including 1, 2 or 3 heteroatoms selected from a group consisting of N, O, P and S, and the remaining atoms may be carbon. That is to say, hydrogens of the cycloalkyl may be substituted for using an alkyl and heteroatom is included. At least one hydrogen of heterocycloalkyl can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or salt thereof, sulfonic acid or salt thereof, phosphoric acid or salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The fused ring may include 7 to 20 atoms in a bicyclic or tricyclic aromatic radical where R_1 and R_2 are linked to form a ring and aryl ring which may be substituted. For example, specific examples include indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl etc. At least one hydrogen of the fused ring can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or a salt thereof, sulfonic acid or a salt thereof, phosphoric acid or a salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_5-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The hetero fused ring may include 6 to 20 atoms in a bicyclic or tricyclic radical including 1, 2 or 3 heteroatoms selected from a group consisting of N, O, P and S, with the remaining atoms in the radical being carbon. The term also means cyclic aromatic radical where heteroatoms in the ring are oxidized or become quaternary to form, for example, an N-oxide or a quaternary salt. Specific examples may include, but are not limited to benzothienyl, cumaryl, quinolinyl, quinoxalinyl, benzopuranyl, benzothiazolyl, benzoisoxazolyl, benzoimidazolyl, indolyl, benzopyridonyl, N-alkyl-2-benzopyridonyl, benzopyrazinonyl, benzopyridazinonyl, benzopyrimidinonyl, benzooxazolonyl, an N-oxide (for example, pyridyl N-oxide, quinoliny N-oxide), or a quaternary salt . At least one hydrogen of the heteroatoms can be substituted for using halogen, hydroxy, nitro, cyano, amino, azido, amido, hydrazine, hydrazone, ester, carboxyl or a salt thereof, sulfonic acid or a salt thereof, phosphoric acid or a salt thereof, or C_1-C_{15} alkyl, alkenyl, alkynyl, cycloalkyl,

cycloalkenyl, cycloalkynyl, C_1-C_{15} heteroalkyl, C_6-C_{18} aryl, C_6-C_{18} arylalkyl, C_2-C_{20} heterocycle, or C_3-C_{20} heteroarylalkyl.

The protein hydrolysis enzyme plays a role in acylating an alcohol enantioselectively in organic solvent in the presence of an acyl donor. The protein hydrolysis enzyme stimulates the stereoselective acylation of an (S)-chiral compound of racemic compounds which is racemized by the metal catalyst. Exemplary protein hydrolysis enzymes may include, but are not limited to stabilized or fixed subtilisin, chymotrypsin, papain, protease from *Aspergillus orygae*, protease from *Aspergillus melleus*, protease from *Streptomyces griseus*, protease from *Bacillus stearothemophilus*, etc. Among the protein hydrolysis enzymes, a protein hydrolysis enzyme with opposite stereoelectivity to lipase, or a lipid hydrolysis enzyme with respect to secondary alcohol can be used in the present invention. An example of a useful protein hydrolysis enzyme with opposite stereoelectivity to lipase is subtilisin. Commercially available stabilized subtilisin includes subtilisin-CLEC. When it is necessary, subtilisin is stabilized in aqueous pyridine solution using polyether-based sufactant. The protein hydrolysis enzymes can be used in an amount of 5 to 1000 mg per 1 mmol of reactive substrate, especially 10 to 300 mg per 1 mmol of reactive substrate.

A hydrogen donor reduces a ketone group of compound having a structure of chemical formula 1 to an alcohol group in the presence of a metal catalyst. Hydrogen donors may include, but are not limited to 2,4-dimethyl-3-pentanol, 2,6-dimethyl-4-heptanol, formic acid, hydrogen. In order to remove the hydrogen easily after production of a chiral ester, it is preferable to use the hydrogen donor under normal pressure. The hydrogen donor is preferably used in an amount of 1 to 10 moles on the basis of 1 mole of the compound having a structure of chemical formula 1.

In some embodiments, since the enzyme catalyst reaction (e.g. protein hydrolysis enzyme) has been affected by solvent in terms of synthesis yield of product and enantioselectivity, the following solvents are preferred: aprotic solvent selected from benzene; toluene; C_5-C_{10} alkane; C_5-C_{10} cycloalkane; tetrahydrofuran; dioxane; C_2-C_{10} dialkylether such as ethylether, diisopropyl ether or t-butyl methylether; C_3-C_{10} alkylate such as ethyl acetate, propyl acetate or ethyl propionate; C_2-C_{10} cyanoalkane such as acetonitrile or propionitrile; C_3-C_{10} dialkyl

ketone such as acetone or methylethyl ketone; dichloromethane; chloroform; carbon tetrachloride, or C_4-C_{10} tertiary alcohol having high hydrophobicity such as tert-butanol or 3-methyl-3-pentanol. Additionally, a room temperature ionic liquid such as 1-methyl-3-ethylimidazolium tetrafluoroborate or 1-methyl-3-butylimidazolium hexafluorophosphate can be also used. In some embodiments, the solvent is preferably controlled so that the concentration of dissolved solute is in a range from 0.1 to 0.8M.

The reaction temperature of dynamic kinetic resolution depends on the kind of the reaction materials and is preferably in a range from 0 to 100°C. In some embodiments, the reaction temperature may be in a range from room temperature to 80°C. When the reaction temperature is less than room temperature, a reaction rate is slow and when it is more than 80°C, the enzyme loses its activity.

Through the reaction outline in step (a), an (S)-chiral ester compound of chemical formula 3 is prepared.

[EXAMPLE]

Example 1

To a Schlenk flask, 3.7mg of $(Ph_4C_5NHCHMe_2)Ru(CO)_2Cl$ and 18µL of t-BuOK solution (1M in THF) was added and dried under the reduced pressure. 1 mL of toluene was added and then agitated for 1 hour. After the toluene was removed under the reduced pressure, 9mg of stabilized subtilisin, 31.8mg of sodium carbonate, 18µL of 1-phenylethanol, 39µL of 2,2,2-trifluoroethylbutyrate and 0.5 mL of THF were added, The mixture was agitated at room temperature for three days. After termination of the reaction, catalyst was filtered, the obtained filtrated solution was concentrated and separated using column chromatography (silica gel, ethyl acetate/hexane = 4:1). Optical purity of the product was measured using high resolution liquid chromatography equipped with a chiral column. The yield of the produced (S)-acetate was 95% and optical purity was 92% enantiomeric excess (herein referred to as ee). (S)-alcohol was obtained by adding (S)-acetate and 2 equivalents of K_2CO_3 to 80% methanol solution and hydrolyzing at room temperature.

$[\alpha]^{25}_D = -87.3$ (c = 1.01, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$, ppm) 7.35-7.28 (m, 5H), 5.90 (q, J = 6.6 Hz, 1H), 2.31 (t, J = 7.4 Hz, 2H), 1.68-1.58 (m, 2H), 1.53 (d, J = 6.6 Hz, 3H), 0.92 (t, J = 7.4

Hz, 3H).

Example 2

To a Schlenk flask, 5.9mg of $(\eta^5\text{-}Ph_4C_4CO)_2H(\mu\text{-}H)(CO)_4Ru_2$, 16mg of stabilized subtilisin, 43 mg of 1-p-chlorophenylethanol, 39μL of 4-chlorophenylbutyrate and 1mL of toluene were added and then agitated at 60°C for three days. After termination of the reaction, the catalyst was filtered, the obtained filtrated solution was concentrated and the product was separated using column chromatography (silica gel, ethyl acetate/hexane = 4:1). Optical purity of the product was measured using high resolution liquid chromatography equipped with a chiral column. The yield of the produced (S)-acetate was 92% and optical purity was 99% ee. The chiral acetate was hydrolyzed using a basic aqueous alcoholic solution and was converted to the corresponding chiral alcohol.

$[\alpha]^{25}_D = -96$ (c=1.03, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$, ppm) 7.33-7.29 (m, 4H), 5.85 (q, J = 6.6 Hz, 1H), 2.30 (t, J = 7.4 Hz, 2H), 1.68-1.58 (m, 2H), 1.50 (d, J = 6.6 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H).

Example 3

To a well-dried Schlenk flask, 7.4mg of $(Ph_4C_5NHCHMe_2)Ru(CO)_2Cl$ and 36μL of t-BuOK solution (1M in THF) was added and dried under the reduced pressure. 0.5 mL of toluene was added and then agitated for 1 hour. After the toluene was removed under the reduced pressure, 18mg of subtilisin-CLEC, 62.6mg of sodium carbonate, 43mg of 1-p-methoxyphenylethanol, 39μL of 4-chlorophenyl butyrate and 0.5mL of THF were added, The mixture was agitated at room temperature for three days. After termination of the reaction, the catalyst was filtered, the obtained filtrated solution was concentrated. The product was separated using column chromatography (silica gel, ethyl acetate/hexane = 4:1). Optical purity of the product was measured using high resolution liquid chromatography equipped with a chiral column. The yield of the produced (S)-acetate was 93% and optical purity was 94% ee. The chiral acetate was hydrolyzed using a basic aqueous alcoholic solution and was converted to the corresponding chiral alcohol.

$[\alpha]^{25}_D = -92.6$ (c=1.01, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$, ppm) 7.29 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.86 (q, J = 6.6 Hz, 1H), 3.80 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.68-1.57 (m, 2H),

1.51 (d, J = 6.6 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H).

Example 4

The reaction procedure was performed in the same manner as in Example 3, except that 1-cyclohexylethanol was reacted in THF instead of 1-p-methoxyphenylethanol. The yield of the produced (S)-acetate was 92% and the optical purity was 98% ee.

$[\alpha]^{25}_{D}$= -1.5 (c=0.98, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$, ppm) 4.77-4.68 (m, 1H), 2.26 (t, J = 7.4 Hz, 2H), 1.76-1.61 (m, 7H), 1.43-1.41 (m, 1H), 1.25-1.14 (m, 6H), 1.05-0.92 (m, 5H).

Example 5

To a Schlenk flask, 10mg of (η^5-indanyl)RuCl(PPh_3)$_2$, 20mg of stabilized subtilisin, 30 mg of 1-cyclohexylethanol, 75 mg of triethylamine, 75μL of 4-chlorophenyl butyrate and 2mL of dichloromethane were added and agitated in the presence of oxygen at 60 °C for three days. After termination of the reaction, catalyst was filtered, the obtained filtrated solution was concentrated and the product was separated using column chromatography (silica gel, ethyl acetate/hexane = 4:1). Optical purity of the product was measured using high resolution liquid chromatography equipped with a chiral column. The yield of the produced (S)-acetate was 80% and the optical purity was 98% ee. The chiral acetate was hydrolyzed using basic aqueous alcoholic solution and was converted to the corresponding chiral alcohol.

$[\alpha]^{25}_{D}$= -1.5 (c=0.98, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$, ppm) 4.77-4.68 (m, 1H), 2.26 (t, J = 7.4 Hz, 2H), 1.76-1.61 (m, 7H), 1.43-1.41 (m, 1H), 1.25-1.14 (m, 6H), 1.05-0.92 (m, 5H).

Example 6

The reaction procedure was performed in the same manner as in Example 1, except that 1-phenyl-2-propanol was used instead of 1-phenylethanol. The yield of the produced (S)-acetate was 77% and the optical purity was 97% ee.

$[\alpha]^{25}_{D}$ = +12.1 (c=1.00, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$, ppm) 7.31-7.18 (m, 5H), 5.13 (q, J = 6.4 Hz, 1H), 2.92 (dd, J_1 = 13.6 Hz, J_2 = 6.8 Hz, 1H), 2.76 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 1H), 2.22 (t, J = 7.4 Hz, 2H), 1.63-1.53 (m, 2H), 1.21 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H).

Example 7

The reaction procedure was performed in the same manner as in Example 1, except that $[(Ph_4C_5NHCHMe_2)Ru(CO)Cl]_2$ was used instead of $(Ph_4C_5NHCHMe_2)Ru(CO)_2Cl$. The yield of the produced (S)-acetate was 82% and the optical purity was 70% ee.

$[\alpha]^{25}_D$= -87.3 (c = 1.01, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$, ppm) 7.35-7.28 (m, 5H), 5.90 (q, J = 6.6 Hz, 1H), 2.31 (t, J = 7.4 Hz, 2H), 1.68-1.58 (m, 2H), 1.53 (d, J = 6.6 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H).

Example 8

The reaction procedure was performed in the same manner as in Example 1, except that 1-phenyl-2-butanol was used instead of 1-phenylethanol. The yield of the produced (S)-acetate was 80% and the optical purity was 98% ee.

$[\alpha]^{25}_D$ = -5.6 (c=1.15, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$, ppm) 7.30-7.15 (m, 5H), 4.98-4.92 (m, 1H), 2.68-2.59 (m, 2H), 2.26 (t, J = 7.4 Hz, 2H), 1.94-1.78 (m, 2H), 1.70-1.62 (m, 2H), 1.24 (d, J = 6.3 Hz, 3H), 0.95 (t, J = 7.4Hz, 3H).

Example 9

The reaction procedure was performed in the same manner as in Example 1, except that 2-octanol was used instead of 1-phenylethanol. The yield of the produced (S)-acetate was 89% and the optical purity was 98% ee.

$[\alpha]^{25}_D$ = +5.7 (c=1.15, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$, ppm) 4.95-4.85 (m, 1H), 2.27 (t, J = 7.4 Hz, 2H), 1.68-1.58 (m, 2H), 1.56-1.37 (m, 2H), 1.27 (s, 8H), 1.19 (d, J = 6.2 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 6.7 Hz, 3H).

Example 10

To a Schlenk flask, 16mg of $[(p\text{-cymene})RuCl_2]_2$, 40mg of stabilized subtilisin, 42 mg of 1-phenylethanol, 150μL of 4-chlorophenyl butyrate and 1.5mL of 1-butyl-3-methylimidazolium hexafluorophosphate ($[BMIM]^+PF_6^-$) were added and agitated at room temperature for five days. After termination of the reaction, catalyst was filtered, the obtained filtrated solution was extracted with chloroform. Extract was concentrated and the product was separated using column chromatography (silica gel, ethyl acetate/hexane = 4:1). Optical purity of the product was measured

using high resolution liquid chromatography equipped with a chiral column. The yield of the produced (S)-acetate was 98% and the optical purity was 89% ee. The chiral acetate was hydrolyzed using basic aqueous alcoholic solution and was converted to the corresponding chiral alcohol.

$[\alpha]^{25}_{D}$= -87.3 (c = 1.01, $CHCl_3$);

^{1}H NMR (300MHz, $CDCl_3$, ppm) 7.35-7.28 (m, 5H), 5.90 (q, J = 6.6 Hz, 1H), 2.31 (t, J = 7.4 Hz, 2H), 1.68-1.58 (m, 2H), 1.53 (d, J = 6.6 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H).

Example 11

The reaction procedure was performed in the same manner as in Example 1, except that 1-triphenylmethyloxy-2-propanol was used instead of 1-phenylethanol. The yield of the produced (S)-acetate was 71% and the optical purity was 99% ee.

$[\alpha]^{25}_{D}$= +16.3 (c = 1.0, $CHCl_3$, deacetylated product);

^{1}H NMR (300MHz, $CDCl_3$, ppm) 7.46-7.24 (m, 15H), 5.17-5.12 (m, 1H), 3.16-3.08 (m, 2H), 2.35 (t, J = 7.4 Hz, 2H), 1.72-1.65 (m, 2H), 1.21 (d, J = 6.5 Hz, 3H), 0.94 (q, J = 5.7 Hz, 3H).

Example 12

The reaction procedure was performed in the same manner as in Example 1, except that 1-benzyloxy-3-chloro-2-propanol was used instead of 1-phenylethanol. The yield of the produced (S)-acetate was 80% and the optical purity was 98.5% ee.

^{1}H NMR (300MHz, $CDCl_3$, ppm) 7.28-7.27 (m, 5H), 5.18 (q, J = 5.2 Hz, 1H), 4.57-4.55 (m, 2H), 3.79-3.61 (m, 4H), 2.34 (t, J = 6.5 Hz, 2H), 1.71-1.61 (m, 2H), 0.94 (q, J = 5.7 Hz, 3H).

Example 13

The reaction procedure was performed in the same manner as in Example 1, except that 1-phenyl-3-hydroxybutyne was used instead of 1-phenylethanol. The yield of the produced (S)-acetate was 90% and the optical purity was 95% ee.

$[\alpha]^{25}_{D}$ = -235.3 (c=0.7, $CHCl_3$);

^{1}H NMR (300MHz, $CDCl_3$, ppm) 7.46-7.39 (m, 2H), 7.34-7.22 (m, 3H), 5,70 (q, J = 6.7 Hz, 1H), 2.33 (t, J = 7.4 Hz, 2H), 1.75-1.63 (m, 2H), 1.58 (d, J = 6.7 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H).

Example 14

To a Schlenk flask, 5.9mg of $(\eta^5\text{-}Ph_4C_4CO)_2H(\mu\text{-}H)(CO)_4Ru_2$, 16mg of

stabilized subtilisin, 62 mg of 3-(1-hydroxyethyl)phenyl butyrate, and 1 mL of toluene were added and agitated in the presence of argon gas at 60℃ for three days. After termination of the reaction, catalyst was filtered, the obtained filtrated solution was concentrated and the product was separated using column chromatography (silica gel, ethyl acetate/hexane = 4:1). Optical purity of the product was measured using high resolution liquid chromatography equipped with a chiral column. The yield of the produced (S)-acetate was 94% and the optical purity was 99% ee. The chiral acetate was hydrolyzed using basic alcohol aqueous solution and was converted to the corresponding chiral alcohol.

$[\alpha]^{25}_{D}$= -95.4 (c = 1, $CHCl_3$);

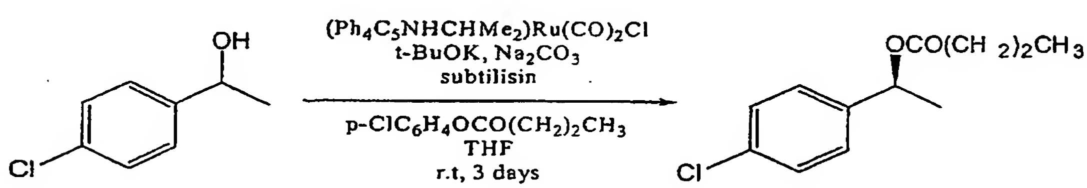
^{1}H NMR (300MHz, $CDCl_3$, ppm) 7.20 (t, J=7.9 Hz, 1 H), 6.91 (d, J = 7.6 Hz, 1 H), 6.82 (s, 1 H), 6.76 (dd, J_1 = 5.5 Hz, J_2 = 1.7 Hz, 1 H), 5.83 (q, J = 6.6 Hz, 1 H), 2.32 (t, J = 7.4 Hz, 2 H), 1.70-1.62 (m, 2 H), 1.51 (d, J = 6.6 Hz, 3 H), 0.94 (q, J = 7.3 Hz, 3 H).

Example 15

To a Schlenk flask, 7.44 mg of $(Ph_4C_5NHCHMe_2)Ru(CO)_2Cl$, 7.5mg of stabilized subtilisin, 47mg of 1-p-chlorophenylethanol, 100 μL of 4-chlorophenyl butyrate and 1 mL of tetrahydrofuran were added and agitated at room temperature for three days. After termination of the reaction, catalyst was filtered, the obtained filtrated solution was concentrated and the product was separated using column chromatography (silica gel, ethyl acetate/hexane = 4:1). Optical purity of the product was measured using high resolution liquid chromatography equipped with a chiral column. The yield of the produced (S)-acetate was 98% and the optical purity was 99% ee.

The reaction scheme to produce the chiral acetate is as follows:

[reaction scheme 1]



The produced chiral acetate was hydrolyzed using basic aqueous alcoholic

solution and was converted to the corresponding chiral alcohol.

Example 16

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that 41 mg of 1-phenyl-2-propanol was used instead of 43 mg of 1-p-chlorophenylethanol.

Example 17

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 3, except that 41.6 mg of 1-(2-puryl)-butene-3-ol was used instead of 43 mg of 1-p-chlorophenylethanol.

Example 18

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 17, except that 1-(cyclohexyl)-butene-3-ol was used instead of 1-(2-puryl)-butene-3-ol.

Example 19

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 5, except that 34 mg of 1-indanol was used instead of 30 mg of 1-cyclohexylethanol.

Example 20

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 1, except that 41.6 mg of 2-octanol was used instead of 43 mg of 1-phenylethanol.

Example 21

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that 2,5-hexandiol was used instead of 1-p-chlorophenylehanol.

Example 22

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 10, except that 1,5-di(hydroxyethyl)pyridine was used instead of 1-phenylehanol.

Example 23

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that methyl-4-phenyl-2-hydroxybutyrate was used instead of 1-p-chlorophenylehanol.

Example 24

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that 2-cyclohexyl-2-hydeoxyacetate was used instead of 1-p-chlorophenylehanol.

Example 25

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that methyl 3-(4-methoxyphenyl)-3-hydroxypropionate was used instead of 1-p-chlorophenylehanol.

Example 26

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that ethyl 3-phenyl-2-hydroxypropionate was used instead of 1-p-chlorophenylehanol.

Example 27

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that t-butyl 5-hydroxyheptanoate was used instead of 1-p-chlorophenylehanol.

Example 28

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that benzyl 3-hydroxybutyrate was used instead of 1-p-chlorophenylehanol.

Example 29

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that 1-triphenylmethyloxy-2-butanol was used instead of 1-p-chlorophenylehanol.

Example 30

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that 1-(5,9-dihydro-6,8-dioxabenzocyclohepene-7-yl-2-propanol was used instead of 1-p-chlorophenylehanol.

Example 31

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that 1-t-butoxy-3-chloro-2-propanol was used instead of 1-p-chlorophenylehanol.

Example 32

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that 1-phenyl-2-chloroethanol was used instead of 1-p-chlorophenylehanol.

Example 33

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that 1-phenyl-2-azidoethanol was used instead of 1-p-chlorophenylehanol.

Example 34

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 2, except that 1-phenyl-2-cyanoethanol was used instead of 1-p-chlorophenylehanol.

Example 35

To a Schlenk flask, 5.9 mg of $(\eta^5\text{-}Ph_4C_4CO)_2H(\mu\text{-}H)(CO)_4Ru_2$, 16mg of stabilized subtilisin, 44mg of 1-oxo-1,2,3,4-tetrahydronaphthalene, 39 μL of 4-chlorophenyl butyrate and 1 mL of toluene were added and agitated at 60°C under 1 atm of hydrogen for three days. After termination of the reaction, catalyst was filtered, the obtained filtrated solution was concentrated and the product was separated using column chromatography (silica gel, ethyl acetate/hexane = 4:1). Optical purity of the product was measured using high resolution liquid chromatography equipped with a chiral column. The produced chiral acetate was hydrolyzed using basic aqueous alcoholic solution and was converted to the corresponding chiral alcohol.

Example 36

Chiral alcohol was obtained by performing the reaction procedure in the same manner as in Example 35, except that 1-phenyl-3-oxobutane was used instead of 1-oxo-1,2,3,4-tetrahydronaphthalene.

Experimental Example 1

The reaction procedure was performed in the same manner as in Example 1, except that 1-phenylethanol was used as a substrate, 9.3 mg of $(Ph_4C_5NHCHMe_2)Ru(CO)_2Cl$, solvent, and acyl donor were used as described in Table 1.

Table 1

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Solvent	Acyl donor	yield (%)	Optical purity (% ee)
2,2,4-trimethylpentane	p-chlorophenyl butyrate	88	80
Toluene	p-chlorophenyl butyrate	86	79
t-butyl methylether	p-chlorophenyl butyrate	93	82
methylene chloride	p-chlorophenyl butyrate	91	87
1,4-dioxane	p-chlorophenyl butyrate	98	84
t-butanol	p-chlorophenyl butyrate	94	91
Tetrahydrofuran	p-chlorophenyl butyrate	98	89
Tetrahydrofuran	Isopropyl acetate	22	71
Tetrahydrofuran	2,2,2-trifluoroethyl acetate	60	52
Tetrahydrofuran	2,2,2- trifluoroethyl butyrate	93	89

[INDUSTRIAL APPLICABILITY]

According to the present invention, (S)-chiral alcohol can be synthesized with high optical purity and high yield by performing dynamic kinetic resolution with respect to an achiral substrate of ketone or a racemic alcohol by the combination of metal catalyst and protein hydrolysis enzyme. The (S)-chiral alcohol is an enantiomer of a chiral alcohol which can be obtained using lipase in conventional dynamic kinetic resolution method.

The method of synthesizing a chiral alcohol is variously applicable to obtain alcohols having various structures, compensating the conventional method using the lipase and can substitute for a conventional chemistry synthesis method or another biochemistry synthesis method.

Further, the (S)-chiral alcohol prepared according to the present invention can be used as an intermediate material of various chiral pharmaceuticals and fine chemicals.